A4 30 ~~102~~. (New) A method according to Claim 29 ~~101~~, wherein the obtaining step is completed within about 60 seconds after the injecting step.

## REMARKS

This Amendment is submitted in reply to the Official Action mailed August 16, 2002 ("the Action"). Claims 1-23 are pending in the action. Claims 24-88 have been withdrawn from consideration as the Action deems that they are properly restricted from examination in the present application. New Claims 89-102 have been added above to form a more complete claim set for the application. Support for same can be found in the application at, *e.g.*, pages 37,48 ($CO_2$), page 33 and original claims (pharmaceutical effectiveness evaluations of therapeutic treatments -- such as drug discovery or clinical trials whether by animal or human), pages 31, 27 (V/Q), pages 23, 24 (surfactant), p. 30 (timing of injection versus image data acquisition), and pages 35, 36, 50, 51(combination injection and inhalation (gas and dissolved $^{129}Xe$ chemical shift) based images).

### I. §112, Second Paragraph

The Action rejects Claims 9 and 20 under §112, second paragraph, for the use of certain terminology. Claim 9 has been amended to depend from Claim 3. Claim 20 has been amended to positively recite the steps of:

> providing a container configured to hold the first injectable quantity of polarized gaseous $^{129}Xe$ therein;
>
> preparing the container to hold the first injectable quantity of polarized gaseous $^{129}Xe$ therein by introducing then expelling $CO_2$ from the container thereby leaving residual traces of $CO_2$ therein; and then
>
> introducing the first quantity of polarized gaseous $^{129}Xe$ into the container prior to the step of injecting.

In view of the foregoing, Applicants respectfully request that these rejections be withdrawn.



A

**II. §103**

The Action rejects the pending claims under §103 as being obvious over one or more references. Claims 1-19 stand rejected over U.S. Patent No. 5,545,396 ("Albert et al.") alone, or combined with U.S. Patent No. 5,811,076 ("Brasch"). Claims 20-23 stand rejected over Albert et al. alone, combined with Brasch, or further in view of U.S. Patent No. 6,315,981 ("Unger"). Applicants respectfully disagree and will address the rejections in the order given.

Claim 1 has been amended to recite that the amount of polarized gaseous $^{129}Xe$ injected is less than about 100 cubic centimeters. Applicants respectfully submit that none of the above cited references teach or suggest injecting this quantity of gaseous $^{129}Xe$ directly into a subject to obtain images.

The Action correctly notes that Albert et al. proposes administering $^{129}Xe$ to a subject for MRI purposes. However, the Action then states that Albert discusses that "various amounts of gas may be used" referring to Example 3, and that the "various other functional limitations in the claims would be inherent characteristics of the methods disclosed by Albert, since Albert administers the same contrast agent, $^{129}Xe$, in the same method, MRI."

In response, Applicants refer the Examiner to Example 3 of Albert et al. A closer reading of the text of Example 3 reveals that this example discusses (mouse) lung-inhalation delivery. Example 3 does not discuss various amounts of directly injectable gas formulations, much less an injectable amount of about 100cc's or less to obtain images, as recited in Claim 1. If the Examiner disagrees, Applicants respectfully request that the Examiner note with specificity where Albert et al. describes this injectable quantity of gaseous $^{129}Xe$.

It should be noted that, to obtain clinically useful images, a sufficient amount of magnetized (polarized) $^{129}Xe$ is needed at a polarization level sufficient to generate the signal. The polarization life of the $^{129}Xe$ is relatively short (under a minute, and typically less than 20-30 seconds). The present invention directly injects the gaseous formulation into a region or system of interest , thereby allowing reduced quantities of the polarized gas to be employed as compared to conventional inhalation based deliveries or dissolved (solubilized) liquid



A

injection deliveries. *See, e.g.*, U.S. 6,426,058 to Pines et al., describing liquid formulations of hyperpolarized gas.

Albert also fails to "inherently" describe the features of dependent claims, such as, but not limited to: low field strength; injection rates; sequential injections; injection volumes; the combination inhalation and the direct injection administration of gaseous $^{129}Xe$; and the use of a surfactant applied *in situ*.

Brasch does not resolve the above-noted deficiencies. Instead, Brasch proposes contrast agents that "must remain in the pool rather than leaving it through such means as diffusion into extravascular compartments or glomerular filtration" (col. 1, lines 33-35). As such, the type of contrast agent proposed by Brasch allegedly has a life that can enhance normal tissues (with MMCM) 5 minutes after administration and 50 minutes later -- purportedly at the same level of enhancement (col. 1, lines 45-50). One of skill in the art would not have combined these references in the manner noted, as the polarized $^{129}Xe$ gas has a short $T_1$ life that is well under 1-minute in the body. Also, $^{129}Xe$ can diffuse or be taken into its local environment(s), such as blood, plasma and/or tissue. Clearly, the claimed method that recites using direct injection of polarized gaseous $^{129}Xe$ is very different from the evaluation method proposed by Brasch. Indeed, Brasch teaches away from using $^{129}Xe$ as claimed for assessing pulmonary embolism because it requires that the contrast agent remain in the blood pool for relatively long periods of time (stating 5 -50 minutes), thereby "eliminating the need for critical timing of the imaging."

Similarly, Unger also fails to resolve the above-noted deficiencies. The Action states that Unger proposes "methods of MRI using gas compositions" and refers to the abstract and Claim 1 in support thereof. However, and notably, Claim 1 of Unger recites agitating an aqueous suspension to produce gas-filled liposomes. Unger clearly fails to teach or suggest the direct injection of gaseous $^{129}Xe$. Further, the surfactant proposed by Unger is added to the solution and used to "stablize" the solution to provide an intact microsphere structure of encapsulated gas for at least 2-3 weeks under normal ambient conditions (col. 12, lines 38-39). However, as is known to those of skill in the art, such long-term stabilization for



A

polarized $^{129}Xe$ would not be required, as the polarized state of the gas deteriorates well in advance of this time period.

In contrast, embodiments of the present invention employ a surfactant to assist in promoting the biocompatibility of the directly injected $^{129}Xe$ polarized gas. *See, e.g.*, pp. 23-24 of the pending application. Indeed, the surfactant is used to destabilize the gas "bubbles", which can reduce the bubble dissipation time in blood and/or blood surface tension. Further, unlike Unger, the present invention does not add the surfactant to a gas which will then sit idly on a shelf for weeks prior to use. Rather, the gas and surfactant are combined *in situ*, at the time of injection. In certain embodiments, the surfactant is separately injected proximate to the injection site of the gas and combined *in vivo* after injection. In summary, one of skill in the art would not have combined Unger with Albert to render the claimed invention obvious because, in contrast to the stabilized surfactant of the suspension in Unger, the surfactant proposed by the pending application is to promote the hyperpolarized gas' adaptation into the body; it is not directed to "extend the encapsulation structure of the solution" or "the polarized *in vivo* life," which will be relatively short.

The Action then states that Unger teaches that the xenon can be mixed with other gases such as $CO_2$ to optimize the gas composition and refers to col. 7, lines 51 et seq. in support thereof. The Action also goes on to state that it would also have been obvious to modify the compositions of Albert to "include Xe mixtures with $CO_2$" to yield gaseous contrast agents which are useful for MRI imaging. Applicants respectfully disagree.

Notably, Unger teaches using $CO_2$ as a major constituent (col. 7, lines 45-58) and describes the use of gases in the form of bubbles in aqueous media (col. 8, lines 29-30). In contrast, the present invention can use $CO_2$ (rather than nitrogen) as a flushing or cleansing agent to remove impurities such as oxygen in the flow path or container. Thus, as contemplated by embodiments of the present invention, only trace amounts of this substance will be present in the injectable formulation. Further, the gases described at col. 7, lines 51 et seq. of Unger, include oxygen, which would deleteriously act to degrade the polarization of the polarized $^{129}Xe$ gas. Applicants respectfully submit that one of skill in the art would not find the instant invention obvious based on the teachings of Unger, even combined with

Albert et al.

**III. Legal Standards**

The legal standards for patentability include novelty and non-obviousness. As affirmed by the Court of Appeals for the Federal Circuit, to support combining references in a §103 rejection, evidence of a suggestion, teaching, or motivation to combine must be clear and particular, and this requirement is not met by merely offering broad, conclusory statements about teachings of references. *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999); *In re Sang Su Lee*, 61 USPQ 2d 1430, 1435 (Fed. Cir. 2002). Further, "[i]t is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements." *Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 43 USPQ2d 1294, 1297 (Fed. Cir. 1997) (emphasis added). The standard of obviousness is not whether, in hindsight, someone would have combined elements to form the invention. *W.L. Gore & Associates v. Garlock, Inc.*, 220 USPQ 303, 312-313 (Fed. Cir. 1983). Applicants reiterate that, properly combined, the cited references fail to teach or suggest the claimed invention. In view of the foregoing, Applicant respectfully requests that the obviousness rejections be withdrawn.



A

**IV. Conclusion**

A marked-up version of the amended claims is attached hereto. Applicants respectfully submit that the application is in condition for allowance which action is requested.

Respectfully submitted,

Julie H. Richardson
Registration No. 40,142

**Correspondence Address:**

20792
PATENT TRADEMARK OFFICE

Tel (919) 854-1400
Fax (919) 854-1401

**CERTIFICATE OF FACSIMILE TRANSMISSION**

I hereby certify that this correspondence is being sent by facsimile transmission to Commissioner for Patents, Washington, DC 20231, at (703) 872-9306 on November 7, 2002.

Rosa Lee Brinson Date of Signature: November 7, 2002



A

**Marked-up Version of Claims**

1. (Amended) A method of screening for the presence of a pulmonary embolism, comprising the steps of:

positioning a subject having a pulmonary region and a blood circulation path including veins and arteries in an NMR system, the subject's pulmonary region having pulmonary veins and pulmonary arteries and associated vasculature defining a pulmonary portion of the circulation path;

injecting a first quantity of polarized gaseous phase $^{129}Xe$ directly into at least one vein of the subject, wherein the first quantity of polarized gaseous phase $^{129}Xe$ is less than about 100 cubic centimeters;

obtaining NMR signal data associated with the injected polarized $^{129}Xe$ in the pulmonary region of the subject, the signal data including information corresponding to the polarized gas introduced in said injecting step;

generating an MRI image having spatial[ly coded] visual representation of the NMR signal data of the injected polarized $^{129}Xe$; and

identifying the presence of at least one condition of blockage, restriction, abnormality, and substantially unobstructed free passage of the pulmonary circulation path.

9. (Amended) A method according to Claim [8] 3, wherein the controlled injection rate is less than about 2 cc/s.

20. (Amended) A method according to Claim 1, further comprising:

providing a container configured to hold the first injectable quantity of polarized gaseous $^{129}Xe$ therein;

preparing the container to hold the first injectable quantity of polarized gaseous $^{129}Xe$ therein by introducing then expelling $CO_2$ from the container thereby leaving residual traces of $CO_2$ therein; and then

introducing the first quantity of polarized gaseous $^{129}Xe$ into the container prior to the step of injecting [wherein said injected quantity of $^{129}Xe$ includes a small amount of $CO_2$ therewith].



A